# On the involvement of prefrontal networks in cognitive ageing

*SPECIAL ISSUE*

# ON THE INVOLVEMENT OF PREFRONTAL NETWORKS IN COGNITIVE AGEING

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ABSTRACT

Normal ageing is associated with a wide variety of disturbances in the structure and function of the human brain. Recent neuroimaging studies suggest that the prefrontal cortex (PFC) is particularly vulnerable to the effects of ageing. These findings are compatible with the so-called 'frontal ageing hypothesis' which has been formulated on the basis of neuropsychological research on non-pathological ageing. We will argue on the basis of recent structural and functional neuroimaging studies that this hypothesis needs to be refined, especially to acknowledge the possible relevance of a distinction between subregions within the PFC. In addition, findings with regard to a differential involvement of grey versus white matter suggest that both have to be considered in relation to age-related cognitive decline. Hence, neural networks and larger systems of interconnected brain regions and the functional activity in these circuits may be more important than specific cortical regions to explain age effects on cognitive functioning. Finally, it is important to consider individual variability due to sex differences and age-extrinsic biomedical factors in research which examines the relationship between brain structure or function and cognitive ageing.

Key words: neuroimaging, prefrontal cortex, medial temporal lobe, functional connectivity, aging, human

## INTRODUCTION

It has been known for long from postmortem research that human ageing is accompanied by a reduction in brain volume (e.g., Haug, 1985; Kemper, 1994; Morrison and Hof, 1997; Uylings et al., 2000). Until recently, this atrophy was thought to be the consequence of neuronal loss (Kemper, 1994). However, with the aid of more modern tools it has been shown that the reduction in total neuronal number is only slight, and atrophy may be rather the result of cell shrinkage, dendritic regression, and a reduction in synaptic density (Haug, 1985; Uylings et al., 2000). The functional significance of these neuronal changes is unclear. At present, there is no direct evidence for a relationship between regional neuronal number and cognitive performance in non-pathological ageing (e.g., Uylings et al., 2000).

Nevertheless, because cognitive processes are dependent upon the integrity of the brain, it does seem likely that changes in brain morphology and/or brain functioning can (partly) account for age-related decreases in cognitive functioning. The neural basis of human cognitive ageing has gained increasing

interest since it became possible to study the structure and function of the brain *in vivo*, using techniques such as computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET).

In this paper we will provide an update of the most recent neuroimaging literature on structural and functional changes in normal, non-pathological brain ageing, while specifically focusing on those regions involved in cognitive functioning. We will put forward the view that cognitive changes in normal, non-pathological ageing are particularly associated with alterations within the prefrontal cortex (PFC). This hypothesis has been proposed since the eighties (e.g., Jolles, 1986; Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999; Braver et al., 2001). However, recent findings suggest that the 'frontal ageing hypothesis' needs to be refined. We will elaborate on this notion by hypothesizing that: (1) age-related brain changes are greatest in specific subregions within the PFC and the neural circuits they are part of, (2) not only grey but also white matter integrity is of major importance for adequate cognitive functioning, and (3) a reduction in 'strategic' information processing capacity, subserved by this prefrontal circuitry, is greatly responsible for age-related cognitive impairments. Furthermore, there is substantial heterogeneity in cognitive ageing trajectories, and a distinction can be made between 'successful' and 'usual' ageing (Rowe and Kahn, 1987). Therefore, we will critically evaluate factors which may possibly modulate the association between brain, ageing and cognition.

## Brain Ageing: Structural Neuroimaging

### *The Limbic-Diencephalic System*

In accordance with postmortem studies, neuroimaging research has consistently shown that the total brain volume decreases as a function of age (e.g., Jernigan et al., 1991, 2001; Coffey et al., 1992, 1998; Pfefferbaum et al., 1994; Blatter et al., 1995; Raz et al., 1997; Courchesne et al., 2000; Resnick et al., 2000; Tisserand et al., 2000b). Just as age effects are not uniform across cognitive functions, regional differences in structural decline of the ageing brain have been found. Because numerous neuropsychological studies have emphasized age-related deterioration of memory processes (e.g., Jolles, 1986; Craik and Jennings, 1992; Verhaeghen et al., 1993; Moscovitch and Winocur, 1995; Prull et al., 2000), the majority of neuroimaging research has focused on the neural substrate of memory. A number of brain regions, together making up the limbic-diencephalic network, play a key role in learning and memory. These include the hippocampal system, parahippocampal gyrus, anterior cingulate, medial thalamus, and mammillary bodies (Zola-Morgan and Squire, 1993; Petri and Mishkin, 1994). Atrophy of the hippocampus and related structures is consistently found in pathological ageing (e.g., De Leon et al., 1989; Fox et al., 1996; Kaye et al., 1997; Jack et al., 1992, 1998, 1999; Visser et al., 1999; Laakso et al., 2000). Also in many studies on normal ageing, a reduction in hippocampal and parahippocampal volume has been found (Murphy et al., 1996; De Leon et al., 1997; Raz et al., 1997; Jack et al., 1992, 1998; Mueller et al., 1998; Tisserand et al., 2000b;

Ylikoski et al., 2000; Pruessner et al., 2001). However, several other studies did not find evidence for age-related volume losses in the hippocampus (Lim et al., 1990; Sullivan et al., 1995; Bigler et al., 1997), or reported that the decrease was not disproportional when compared to tissue loss in other brain regions (Raz et al., 1997; Tisserand et al., 2000b). Most of these studies have been cross-sectional and therefore provide only indirect evidence for age-related atrophy. Several studies found a significant longitudinal decrease in medial temporal lobe (MTL) volume in individuals over 65 years of age (Kaye et al., 1997; Jack et al., 1998; Mueller et al., 1998), whereas in two studies in adult subjects across the age range, no evidence was found for longitudinal changes in the volume of the temporal lobes as a whole (Pfefferbaum et al., 1998; Resnick et al., 2000).

Whereas age effects on MTL regions have been fairly well documented, only a small number of studies have focused on other limbic-diencephalic structures, with conflicting results. A significant reduction in the volume of the thalamus has been reported by some (Murphy et al., 1996; Van der Werf et al., 2001), but not by others (Jernigan et al., 1991, 2001). Likewise, while we found an age-related decrease in anterior cingulate volume (Tisserand et al., 2001, 2002), others did not (Jernigan et al., 1991; Raz et al., 1997). Finally, with respect to the volume of the mammillary bodies, age-related losses have been found in some studies (Raz et al., 1992; Sullivan et al., 1999), but not in others (Tisserand et al., 2000a).

Several studies with healthy elderly subjects have tried to relate these reductions in limbic-diencephalic volume to cognitive performance, with mixed results. For instance, one research group found that hippocampal volume was predictive of performance on word list recall (Golomb et al., 1994) and subsequent decline on memory tests after a period of four years (Golomb et al., 1996), while others failed to find a relationship with test performance after adjusting for age effects (Raz et al., 1998; Petersen et al., 2000; Tisserand et al., 2000b; Ylikoski et al., 2000) or even found an inverse relationship (Köhler et al., 1998; Foster et al., 1999). Interestingly, one study found an age-independent correlation between thalamic volume and speed of information processing (but not memory functioning) in young but not in older subjects (Van der Werf et al., 2001). This suggests that in healthy young adults, larger thalamic volume may be favourable for fast processing of information, while variance in volume associated with increasing age is not predictive of task performance. Perhaps in elderly subjects, volume decreases are linked to cognitive deterioration only when pathological mechanisms are involved (DeCarli et al., 1994; Köhler et al., 1998; Foster et al., 1999; Kabani et al., 2002). Alternatively, a lack of associations between brain volume and performance in older subjects may be due to an increase in the variance of these measures with age (e.g., Blatter et al., 1995; Jernigan et al., 2001). This differential influence of age on the direction of brain-behaviour associations may explain why most studies with subjects across the adult age range have not found an effect of brain volume on cognitive performance.

### *The Frontal-Striatal-Thalamic System*

Studies involving patients with focal brain damage (e.g., Janowsky et al., 1989; Stuss et al., 1994; Shimamura et al., 1995) and neuroimaging experiments

with healthy individuals (e.g., Tulving et al., 1994; Kapur et al., 1996; Smith et al., 1996; reviewed by Fletcher and Henson, 2001) suggest that frontal regions may play an equally important role as the limbic system in certain memory domains, especially those involving active organization of the memory contents. The frontal cortex plays a crucial role in a second cognitive brain circuit, which is designated the frontal-striatal-thalamic network (Alexander et al., 1990; Cummings, 1993; Rubin, 1999). This network actually consists of five parallel circuits, three of which are involved in complex behaviour and cognition, such as working memory and executive functions. These circuits typically include a region within the frontal lobes, projecting to striatal structures, which are connected through the globus pallidus and substantia nigra to the thalamus. This structure in turn projects back to the frontal regions (Alexander et al., 1990; Cummings, 1993). In comparison to the literature on limbic-diencephalic structures, reports on age-related changes within the frontal-striatal circuit are relatively limited in number. Nonetheless, there is evidence for disproportionate volume losses within the frontal lobes (Coffey, 1993; Cowell et al., 1994; Raz et al., 1997; Salat et al., 1999, 2001; Tisserand et al., 2001, 2002), the thalamus (Van der Werf et al., 2001) and the striatum (Gunning-Dixon et al., 1998; Rubin, 1999). In an extensive review of the literature on correlations between regional cerebral volume and age, Raz (2000) found that the brain regions most affected are the PFC and the striatum (caudate and putamen). Longitudinally, the cortical region with the greatest volume reduction over a 5-year period was found to be the PFC (Pfefferbaum et al., 1998). Unfortunately, no subcortical grey matter structures (such as the striatum or thalamus) were measured in this study.

Only few studies examined the association between atrophy in this circuit and cognitive decline. A weak relation was found between prefrontal volume and working memory performance (Raz et al., 1998), and cognitive flexibility (Hänninen et al., 1997), but this association was no longer significant when age effects were adjusted for (Raz et al., 1998). As mentioned earlier, in young individuals, the volume of the thalamus was found to be predictive for processing speed (Van der Werf et al., 2001).

### *White Matter Changes*

Whereas an age-related decline in regional grey matter volume has been observed in most imaging studies (Jernigan et al., 1991, 2001; Pfefferbaum et al., 1994; Blatter et al., 1995; Raz et al., 1997; Courchesne et al., 2000; Resnick et al., 2000), starting already in young adults (Blatter et al., 1995; Gur et al., 1999; Courchesne et al., 2000), there is still debate as to the relative contribution of white matter to volume decreases in ageing. Postmortem findings have suggested that white matter atrophy is even more extensive than grey matter loss (e.g., Kemper, 1994). Likewise, several MRI studies have reported age-related loss of white matter (Guttmann et al., 1998; Resnick et al., 2000; Jernigan et al., 2001), especially in the frontal lobes (Raz et al., 1997; Salat et al., 1999; Jernigan et al., 2001). However, other imaging studies have not found evidence for global white matter volume decreases (Jernigan et al., 1991; Pfefferbaum et

al., 1994; Blatter et al., 1995; Raz et al., 1997). It has been suggested that white matter volume remains relatively stable until high age, after which a rapid decline occurs (Salat et al., 1999; Tisserand et al., 2002).

Regardless of whether or not the overall white matter volume decreases, it is not to say that no structural changes take place within the white matter with advancing age. In fact, a very prominent feature noted in brain imaging is an age-related increase in white matter lesions: small damaged foci, which nevertheless can be quite readily observed on CT and MRI (e.g., Jernigan et al., 1991, 2001; Boone et al., 1992; Ylikoski et al., 1993; Breteler et al., 1994; DeCarli et al., 1995; Longstreth et al., 1996). White matter lesions have been found to co-occur with, and to be even more common than, grey matter atrophy (Ylikoski et al., 2000; Jernigan et al., 2001). These lesions are associated with cognitive deficits and may be implicated in the age-related decline in cognitive performance (Longstreth et al., 1996; Gunning-Dixon and Raz, 2000). The associations between severity of the lesions and cognitive decline are particularly evident on tests measuring attention and processing speed (e.g., Boone et al., 1992; Ylikoski et al., 1993; DeCarli et al., 1995; De Groot et al., 2000). Little is known about regional specificity, although there is some evidence that white matter lesions are most frequent in the frontal lobes (De Leeuw et al., 2001; Jernigan et al., 2001).

Other evidence for an age-related decrease in white matter integrity comes from MRI studies which have used diffusion tensor imaging (DTI). DTI is a recently developed technique which provides an index of microstructural tissue properties by assessing the orientation of diffusion of water molecules within the white matter (Pierpaoli et al., 1996). A reduction in this diffusion tensor (implying a disruption of the white matter tracts) has been found with advancing age (Nusbaum et al., 2001; O'Sullivan et al., 2001; Sullivan et al., 2001; Abe et al., 2002), with the strongest effects within the frontal white matter ( O'Sullivan et al., 2001; Sullivan et al., 2001; Abe et al., 2002). Together with the increase in white matter lesions, these findings of changes in the organisation of white matter pathways in normal ageing have been interpreted in terms of increased vulnerability of older individuals for cognitive dysfunction due to (sub)cortical disconnection.

## *Conclusion*

To summarize, ageing is associated with decreased grey matter volume, and the volume reductions are greatest for the frontal lobes, striatum, and thalamus. On the other hand, changes within the limbic-diencephalic memory system appear to be relatively mild. Age-related changes within the white matter have also been observed, particularly as an increase of white matter lesions, with the highest frequency in the frontal lobes. As the grey matter structures mentioned are strongly interconnected, it is plausible that volume losses within the frontal-striatal-thalamic circuit may contribute to age-related cognitive decline. Generally, however, volume decreases within grey matter structures have not been found to be predictive of deterioration in specific cognitive functions. On the other hand, lesions within the white matter have been associated with aspecific dysfunctions

such as reduced information processing speed and attention. As the white matter contains the fibers which connect the various cortical and subcortical grey matter structures, these white matter lesions may disrupt the neural transmission in functional networks, resulting in performance decreases.

## Brain Ageing: Functional Neuroimaging

### *General Findings in Neuroimaging Studies*

The fact that only few associations have been found between structural brain changes and cognitive performance in normal ageing, may be due to the fact that changes in brain structure as such do not have a straightforward relation with brain function. A more direct way to link brain and behaviour is by using functional imaging methods. In contrast with the large number of studies of age-related structural brain changes, the field of research which investigates functional changes is still relatively young, although the number of publications is increasing rapidly (see for some recent reviews on functional imaging studies and ageing: Cabeza, 2000, 2002; Grady and Craik, 2000; Raz, 2000). In the present paper we will mainly focus on changes within the PFC and the MTL.

Functional neuroimaging studies have examined the effect of age both at rest and during cognitive test performance. At rest, a moderate decrease in both regional cerebral blood flow and metabolic rate has consistently been found, with differential sensitivity of the frontal lobes (Kuhl et al., 1982; De Leon et al., 1987; Leenders et al., 1990; Martin et al., 1991; Loessner et al., 1995; Moeller et al., 1996; Petit-Taboué et al., 1998; Garraux et al., 1999), a pattern which is already evident in middle-aged adults (Schultz et al., 1999). Findings with respect to the MTL are inconsistent, but in general, no disproportionate change in activity has been reported (save by Martin et al., 1991).

The majority of activation studies on ageing have focused on explicit memory and working memory. This is not surprising, given the evidence that age-related cognitive deficits are particularly evident in these domains (Jolles, 1986; Craik and Jennings, 1992; Moscovitch and Winocur, 1992; Verhaeghen et al., 1993; Salthouse, 1996; Parkin and Java, 2000; Prull et al., 2000). Experiments that have examined age-related differences in brain activation patterns during more basic cognitive functions such as visual perception (Grady et al., 1994; Horwitz et al., 1995; Ross et al., 1997), motor function (Calautti et al., 2001), and attention (Johannsen et al., 1997; Madden et al., 1997) are still relatively limited in number. Although in this review we will concentrate on higher cognitive functions, it is important to bear in mind that already at the lowest level of information processing age-related changes occur (due to real functional differences or a lower signal-to-noise ratio in older subjects, e.g., D'Esposito et al., 1999). Because in most functional imaging studies a certain experimental condition is compared to a baseline condition, baseline differences in activation can substantially influence the results of group comparisons.

### *Brain Activity and Memory Tasks*

Neuropsychological research has consistently found that working memory capacity, which involves the temporal storage and processing of information, is strongly reduced by increasing age (e.g., Kirasic et al., 1996; Park et al., 1996; Parkin and Java, 2000). During working memory tasks, young individuals tend to activate regions within the lateral and medial prefrontal and posterior parietal cortex, and this activity is asymmetrical depending on the stimulus material. Verbal tasks have been associated with predominantly left-hemisphere activity, whereas spatial tasks elicit mainly activity in the right hemisphere (Smith et al., 1996; Smith and Jonides, 1997; D'Esposito et al., 1998; Reuter-Lorenz et al., 2000). In elderly subjects, this lateralization in frontal regions is less outspoken and bilateral activity patterns during both spatial and verbal working memory tasks occur (Reuter-Lorenz et al., 2000; Cabeza, 2002). Furthermore, apart from such a hemispheric distinction, task-dependent differences in activity in ventrolateral versus dorsolateral PFC have been observed in young subjects (Braver et al., 1997; Cohen et al., 1997; Manoach et al., 1997; Rypma and D'Esposito, 1999; Stern et al., 2000). According to the so-called two-stage model of working memory, the ventrolateral PFC is principally concerned with maintaining information in working memory, while the dorsolateral PFC is recruited when active manipulation of the stored items is required (Petrides, 1995; Owen et al., 1996, 1998). Because elderly are more impaired on tasks which require manipulation and executive control than those requiring only temporal storage in working memory (as reviewed by Verhaeghen et al., 1993), one might expect the greatest age-related differences in brain activity to be located within the dorsolateral PFC. Indeed, whereas task-related activity was noted both in dorsolateral and ventrolateral PFC across groups, an age-related difference in activation during various working memory tasks was found in the dorsolateral but not ventrolateral PFC (Nagahama et al., 1997; Esposito et al., 1999; Rypma and D'Esposito, 2000). In the experiment by Rypma and D'Esposito (2000) the effects of ageing on the various stages of working memory (encoding, storage, and retrieval) were explicitly investigated. Differences between young and older subjects were found only at the retrieval stage, i.e. older individuals activated the dorsolateral PFC to a lesser degree. Other studies, however, did not find evidence for such a differential age effect on the dorsolateral PFC (Grady et al., 1998a; Mencl et al., 2000; Mitchell et al., 2000). Interestingly, in each of these latter reports an age-related difference was instead consistently observed in (the anterior part of) the ventrolateral PFC, as well as in the MTL, areas which the older subjects activated to a lesser degree than the young, or did not activate at all. To conclude, there is conflicting evidence as to whether ageing reduces task-related activity in specific regions within the PFC.

Apart from a working memory decline, a considerable age-related deterioration can also be observed on tasks measuring explicit memory, i.e. the conscious recollection of past events and facts (Graf and Schacter, 1985). A number of studies have considered age-related changes in brain activity on explicit memory tasks. PET and fMRI experiments have shown that in young

subjects, encoding tasks (either verbal or nonverbal) generally elicit left prefrontal, bilateral medial temporal and fusiform gyrus activation (e.g., Kapur et al., 1996; Nyberg et al., 1996a; Fletcher et al., 1998; Kopelman et al., 1998). The most consistent difference between young and older adults during encoding has been found in prefrontal activity. Older subjects either fail to activate the left frontal cortex (Grady et al., 1995), or exhibit reduced activity (Cabeza et al., 1997a, b; Grady et al., 1998b; Anderson et al., 2000). Findings with regard to age effects on posterior brain regions are less consistent. Medial temporal areas have been reported to be equally (Schacter et al., 1996; Madden et al., 1999), or less (Grady et al., 1995) activated during encoding in elderly.

Whereas during encoding prefrontal activity is mostly left-lateralized, the opposite hemisphere is activated during retrieval, a pattern described as the hemispheric encoding/retrieval asymmetry, HERA (Tulving et al., 1994). Other regions involved in retrieval include the anterior cingulate, medial temporal and parietal lobes, and the cerebellum (e.g., Andreasen et al., 1995; Nyberg et al., 1996b; Rugg et al., 1997; Schacter et al., 1997; Wagner et al., 1998). Again, older adults differ from their younger counterparts particularly in prefrontal activity, that is, they show a more bilateral activation pattern (Schacter et al., 1996; Cabeza et al., 1997a, b; Madden et al., 1999; Anderson et al., 2000; Cabeza, 2002). With respect to the MTL, generally, no age-related difference in activity has been reported (Schacter et al., 1996; Madden et al., 1999; Cabeza et al., 2000; but see Bäckman et al., 1997).

### *Brain Activity and Effortful Tasks*

How can we interpret these findings, in particular, how can we explain the fact that prefrontal activity in elderly has been found to be decreased under some circumstances (e.g., Grady et al., 1995) and increased under other (e.g., Madden et al., 1999)? One explanation for age-related differences in left prefrontal activity is that it reflects recruitment of additional resources to cope with task demands, i.e. extra effort. That is, when task difficulty increases, an increase in prefrontal activation is likely to occur. This pattern has been found in studies with young subjects, using both working memory (Braver et al., 1997; Manoach et al., 1997; Rypma and D'Esposito, 1999; Tisserand et al., 2000a) and episodic memory tasks (as reviewed by Nolde et al., 1998). Moreover, practice (i.e., a decrease of conscious processing) has been associated with a decrease in frontal activity (Raichle et al., 1994; Garavan et al., 2000; Jansma et al., 2001). This 'prefrontal-effort hypothesis' may also apply to older individuals. On the neural level, it has been described in terms of compensation: by recruiting additional prefrontal regions older adults may prevent their performance from declining (e.g., Grady et al., 1994; Cabeza et al., 1997a; Grady, 2000; Mencl et al., 2000; Cabeza, 2002). This view is supported by a study by Anderson et al. (2000), who found that left prefrontal activity was reduced similarly by ageing and by a divided attention task, suggesting that increasing age and effortful cognitive processing put an equal claim on the available attentional resources. Furthermore, in a study which compared performance on a dual-task with performance on either task alone (Smith et al., 2001) it was found that both older subjects and young poor

performers activated the left PFC during a demanding dual-task, whereas young good performers did not. Additional evidence for the effort hypothesis comes from an experiment which compared a simple (recognition) and difficult (temporal order) retrieval task (Cabeza et al., 2000). It was found that during the difficult task version young subjects activated the right PFC more than the left, whereas the older subjects had stronger activity in the left PFC. No age differences were found in posterior regions. A final source of evidence for the effort hypothesis is the finding that reduced frontal activity is often accompanied by poorer task performance and/or longer reaction times in older subjects (Grady et al., 1998a; Madden et al., 1999; Grady and Craik, 2000; but see Rypma and D'Esposito, 2000). These findings support the view that older adults make an extra effort to perform as well as young subjects on cognitive tasks, and this is reflected on the functional level as an increase in (left) prefrontal activity.

An alternative (albeit not incompatible) explanation is that age-related changes in frontal activity are part of a more general reduction in the efficiency of neural circuits, and recruitment of brain areas which are not essential to the task (e.g., Cabeza et al., 1997a; Esposito et al., 1999; Madden et al., 1999; McIntosh et al., 1999). This reduced neural efficiency has been ascribed to a decline in frontal inhibitory control over posterior brain regions (Hasher and Zacks, 1988; Esposito et al., 1999; Grady, 2000; Cabeza, 2002). For instance, whereas young individuals were found to recruit a network in which there was strong inhibitory feedback from frontal to posterior regions during a short-term memory task, older subjects' neural connections were much weaker and hardly displayed such inhibitory influences (Della-Maggiore et al., 2000). According to this 'decreased neural efficiency' view, an increase in activity is not necessarily beneficial, as suggested by the effort hypothesis, but rather may be detrimental for cognitive functioning. This interpretation can be tested by relating brain activation patterns to behaviour. Reductions in the efficiency of a given neural circuit may lead to slowing of cognitive processes, which would be reflected as a positive correlation between brain activity and reaction times. Support for this hypothesis comes from a study which showed that in young participants, increases in activity within frontal as well as occipital and medial temporal regions were associated with shorter reaction times, whereas in older adults increased activity in these areas was related to slower performance (Grady et al., 1998a). Other evidence for reduced neural efficiency in the elderly is provided by the study by Madden et al. (1999) in which it was shown that both in young and old subjects, the best predictor of reaction times was a right prefrontal region, while in the old group several additional, non-frontal regions were found to also predict performance.

## *Conclusion*

In sum, ageing is – generally – accompanied by global decreases in brain activity, both at rest and during cognitive test performance. The most evident changes occur within the PFC. In addition to a general decrease in baseline activation, a particular pattern of task-related activation has been found in elderly, where both decreased and increased frontal activity have been noted. Age effects on brain activity in posterior regions are less clear. An increase in

frontal activity possibly reflects an extra effort to cope with task demands, whereas a decrease may be related to a reduction in neural efficiency. However, discrepancies between imaging studies remain and no explanation has yet been proposed with respect to sources of variability. The next paragraph is devoted to the evaluation of factors which are possibly important in this respect and which ought to be considered in future studies into the relationship between age, brain, and cognition.

## Towards a Differentiation of Age Effects on the Prefrontal Cortex

### *Cognitive Differentiation and Neural Networks in Relation to Ageing*

In this paper the main focus has been on age effects in memory-related and higher cognitive functions, i.e., working memory, executive functions, and explicit learning and retrieval. Although age decrements are very prominent on these functions (Jolles, 1986; Craik and Jennings, 1992; Moscovitch and Winocur, 1992; Verhaeghen et al., 1993; Salthouse, 1996; Parkin and Java, 2000; Prull et al., 2000; Braver et al., 2001), these changes cannot be considered in isolation. The role of basic cognitive functions such as processing speed and attention should also be taken into account. These factors have been found to explain a large part of age-related memory deterioration (Verhaeghen et al., 1993; Kirasic et al., 1996; Park et al., 1996; Salthouse, 1996; Earles et al., 1997; Parkin and Java, 2000; Zacks et al., 2000). It has even been suggested (e.g., Salthouse, 1996; Earles et al., 1997) that age-related decline of memory functioning is secondary to reduced processing speed. Reduced information processing speed may explain problems in memory encoding and retrieval because this mental slowing can lead to superficial processing and inefficient strategies where elaboration is required (Jolles, 1986). Interestingly, a strong association between white matter lesions and slowing on information processing tasks in normal, healthy elderly has been found (Ylikoski et al., 1993; DeCarli et al., 1995; De Groot et al., 2000). These results strengthen the notion that the connections between cortical and subcortical regions have to be intact to guarantee the efficiency of the communication between them (e.g., McIntosh, 1999, 2000; Greenwood, 2000; Braver et al., 2001).

The suggestion that it is of importance to adopt a more ‘dynamic’, and multidimensional view with respect to the relationship between cognitive functioning and regions within the brain has further been stressed in the recent literature. Mesulam (1998) described five brain circuits, each with a different function in information processing and cognition. Basic premise is that cognitive functions are composed of various subprocesses, each requiring the integrity of multiple brain regions. Besides the two networks described earlier in the present paper (designated the explicit memory and working memory-executive function circuits), there are three additional networks involved in spatial awareness, language, and face-object recognition. It is argued that for adequate functioning, activation of each network is required. ‘Transmodal nodes’ in the brain connect the various circuits, thereby offering a possibility to combine their information.

Interestingly, there is a model which has applied the idea of such an involvement of multiple brain systems to account for the pattern of cognitive impairments in ageing (Moscovitch and Winocur, 1992, 1995). This model suggests that age does not affect memory *per se*, but rather influences the capacity to efficiently process information in general. The model distinguishes between two types of explicit memory: associative and strategic. The strategic system consumes more attentional resources than the associative system, and therefore it is more sensitive to an age-related reduction of these resources (Craik and Byrd, 1982). The associative component involves the relatively automatic encoding, storage and retrieval of information and is largely dependent on MTL structures. The more conscious and 'intelligent' control over this automatic, associative system, both at input and output, is provided by the frontal lobes, which are involved in the strategic processing of information (Moscovitch and Winocur, 1992, 1995). This theory offers an explanation for the finding that, although both medial temporal and frontal regions are required for explicit memory, age effects are more pronounced on 'strategic' memory tasks (e.g., free recall), than on tasks that rely primarily on the associative system (e.g., recognition). It also predicts that older individuals are slower and make more errors particularly on demanding cognitive tasks, such as those requiring working memory and executive functions. Finally, this view coincides with the evidence that the integrity of the frontal lobes is more sensitive to ageing than that of the MTL.

It follows from this line of argument that even when the same brain regions are involved in task performance in different age groups, their functional interactions may be different. This finding of altered connectivity in the brains of elderly has been reported many times in neuroimaging experiments with various different paradigms (Grady et al., 1994, 1995; Cabeza et al., 1997a, 1997b; Grady, 1998; Esposito et al., 1999; Madden et al., 1999; McIntosh et al., 1999; Della-Maggiore et al., 2000). For example, an age-related difference in connectivity between the PFC and the MTL has been found (Grady et al., 1995; Esposito et al., 1999; Della-Maggiore et al., 2000). These findings suggest that in order to understand the relation between activity in a given brain region (e.g., PFC) and task performance, the region needs to be considered in the context of other, simultaneously activated and functionally connected, brain areas (McIntosh, 1999; Della-Maggiore et al., 2000; Braver et al., 2001).

### *Structural Differentiation within the Prefrontal Cortex*

The PFC is a large and heterogeneous region, and can be subdivided in a number of functionally distinct areas. A broad subdivision has been proposed in an orbital, lateral and medial part (Fuster, 1980; Stuss and Benson, 1986; Cummings, 1995). The lateral PFC is thought to be mainly involved in 'higher' cognitive processes such as those related to memory, behavioural planning, and response inhibition. The medial part (especially the anterior cingulate) plays a role in attention and motivation, and the orbital part in emotional and social behaviour, and impulse control (e.g., Cummings, 1995; West, 1996). Recent functional neuroimaging studies suggest that even smaller distinctions should be

made (e.g., Petrides, 1995; Owen et al., 1996, 1998; Smith and Jonides, 1999; Elliott et al., 2000). For example, as mentioned before, within the lateral PFC a dorsal and ventral part can be distinguished.

It is of relevance in this respect, that each of these prefrontal regions has its own projection areas, and forms a part of a different neural circuit. As mentioned before, all three regions project to the striatum and receive projections from the thalamus. Furthermore, the lateral PFC has reciprocal connections with the orbitofrontal cortex and the anterior cingulate, as well as with posterior association areas and the MTL. The orbitofrontal cortex and anterior cingulate have afferent and efferent connections particularly with the amygdala (Alexander et al., 1990; Cummings, 1995; Petrides, 1995). Despite the fact that such a notion of prefrontal differentiation has been adopted for a number of years, studies which have considered selective structural or functional effects of age on prefrontal subregions are scarce. Ageing may selectively affect particular prefrontal areas while sparing others (Kemper, 1994; Raz et al., 1997; Uylings et al., 2000; Xu et al., 2000; Salat et al., 2001; Tisserand et al., 2001, 2002), and this in turn may have consequences for the specific cognitive functions and networks in which these brain regions are involved. Because of the importance of the PFC in cognitive ageing (e.g., Jolles, 1986; Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999; Braver et al., 2001), future imaging studies have a task in differentiating between frontal regions and their specific functions in relation to ageing.

### *Subject Selection: the Role of Sex Differences and Age-Extrinsic Factors*

An issue which has received insufficient attention is the difference in brain ageing between men and women. For instance, the rate of global atrophy has been found to be higher for men than for women (Gur et al., 1991, 1999; Blatter et al., 1995; Murphy et al., 1996; Coffey et al., 1998; Xu et al., 2000). Furthermore, there are indications that whereas in men atrophy is especially marked in frontal and temporal regions (Cowell et al., 1994; Murphy et al., 1996; Xu et al., 2000), in women volume decreases are more pronounced in the parietal lobes and hippocampus (Murphy et al., 1996; Pruessner et al., 2001). However, not all studies have found age-related sex differences in regional brain volumes (e.g., De Leon et al., 1997; Raz et al., 1997; Coffey et al., 1998; Tisserand et al., 2000b, 2002). With respect to white matter lesions, overall sex differences have been reported but no interaction with age (Longstreth et al., 1996; De Groot et al., 2001; De Leeuw et al., 2001), except in one large sample, in which a greater age-related increase in white matter lesions in females was found (Yue et al., 1997). At the functional level, differences between the sexes have been observed. Women were found to have a greater age-related metabolic decline than men in the thalamus and hippocampus (Murphy et al., 1996). However, others have failed to find such sex differences (e.g., Loessner et al., 1995).

In functional activation studies, the effect of sex has received only little attention (save in Nyberg et al., 2000), and to our knowledge, possible interactions between age and sex during task performance have not yet been considered at all. This is a major issue, because different trajectories for age-

related cognitive decline may exist for healthy men and women (Elias et al., 1997; Laursen, 1997).

Another issue with great importance for the interpretation of age effects on brain structure and function pertains to possible differential decline due to age-extrinsic biomedical factors. The idea that there are various patterns in cognitive ageing trajectories was originally put forward by Rowe and Kahn (1987). These authors distinguished between 'usual' and 'successful' ageing. Successful ageing reflects the situation in which only age-intrinsic factors contribute to a decline in cognitive function. Usual ageing, the most common pattern, is also determined by age-extrinsic factors. For instance, blood pressure increases as a function of age (e.g., Van Boxtel et al., 1996; Rigaud and Forette, 2001), which is of importance as hypertension is associated with abnormalities in cerebral white matter, and both factors have been associated with cognitive decline in older individuals (Skoog, 1994). Furthermore, neurochemical changes occur in the ageing brain, such as decreases in striatal dopaminergic function, and these losses have been associated with cognitive impairments (Volkow et al., 1998; Bäckman et al., 2000; Braver et al., 2001). In addition, long-term exposure to elevated cortisol levels in elderly individuals was found to be related to smaller volume of the hippocampus and impaired performance on memory tests (Lupien et al., 1998). Other age-extrinsic factors which have been associated with cognitive decline include diabetes mellitus, chronic respiratory disease (Van Boxtel et al., 1998), mild sensory impairments (Van Boxtel et al., 2000), and so-called 'biological life events' such as mild brain trauma (Houx et al., 1993; Klein et al., 1996).

Finally, in an attempt to link the issues of sex differences and age-extrinsic factors, it is interesting to consider the effect of steroid hormones on the ageing brain. The interest in the effect that these hormones can exert on the structure and function of the brain has increased now that hormonal replacement therapies have become widespread (e.g., Hogervorst et al., 2000). In particular, the neuroprotective effect of estrogens on the brain (e.g., Sherwin, 1998) may explain attenuation of sex differences in brain volume losses in older individuals (Pruessner et al., 2001). Moreover, estrogen replacement therapy in postmenopausal women has a beneficial effect on brain activity during task performance (Berman et al., 1997; Shaywitz et al., 1999).

Given these findings, it is of importance for cognitive ageing research to acknowledge the possible influence of individual variability due to age-extrinsic factors. In this respect, a dilemma lies within the selection criteria used when sampling healthy older subjects for inclusion in ageing studies: hould they be perfectly healthy (and thus: successfully ageing), or should they be representative for the general elderly population (normally ageing)? Discrepancies between the results of functional imaging studies of cognitive ageing may therefore be due to differences in subject selection criteria.

## Concluding Remarks

In this paper, we have evaluated current knowledge about structural and functional changes within the ageing brain, and the possible relationship

between these changes and cognitive decline. Although the neuropsychological literature on the effects of age on cognitive functioning is vast, the application of neuroimaging techniques in this field of research is a relatively recent development. In order to understand the neural mechanisms underlying cognitive ageing much research still has to be conducted. Nevertheless, the close association between ageing, cognition and the frontal lobes has been noted by various authors (e.g., Jolles, 1986; Moscovitch and Winocur, 1995; West, 1996; Phillips and Della Sala, 1999; Braver et al., 2001), and the present review again stresses the importance of the PFC in cognitive ageing. Age-related atrophy is most apparent in this region (e.g., Raz et al., 1997; Tisserand et al., 2002) and the areas to which they are reciprocally connected, i.e., striatum and thalamus (Gunning-Dixon et al., 1998; Van der Werf et al., 2001). In contrast, only moderate volume reductions have been reported within limbic regions (e.g., Raz et al., 1997; Tisserand et al., 2000b). Furthermore, differences between young and older individuals in functional imaging studies, both at rest and during cognitive performance, have been observed most consistently within the frontal lobes (e.g., Loessner et al., 1995; Moeller et al., 1996; Cabeza et al., 1997a, b; Petit-Taboué et al., 1998; Madden et al., 1999; Reuter-Lorenz et al., 2000). Older subjects tend to exhibit a less lateralized activation pattern than their younger counterparts on a variety of tasks (Cabeza, 2002). Nonetheless, it is of importance to note that several researchers have criticized the frontal ageing hypothesis (e.g., Rubin, 1999; Greenwood, 2000; Braver et al., 2001). They have stressed that structural and functional changes also occur in non-frontal regions (Greenwood, 2000; Braver et al., 2001), and that for adequate cognitive functioning the integrity of all the structures involved in that particular function is required (Rubin, 1999). Of course it is untenable to suggest that age-related cognitive impairments exclusively result from prefrontal declines. In fact, we have tried to argue that cognitive impairments should no longer be considered to be the result of structural or functional alterations within one particular brain region. Just as cognitive functions are made up of a number of subprocesses, brain regions are clustered in networks, interconnected by white matter pathways, all of which together allow cognitive processes (Mesulam, 1998; McIntosh, 2000). It seems that disruptions in prefrontal networks, with their specific role in strategic information processing and in modulating neural activity throughout the brain, are crucial for the understanding of age-related cognitive impairments.

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